NO Cations as Highly Efficient Catalysts for Carbon–Carbon Bond Forming Reactions

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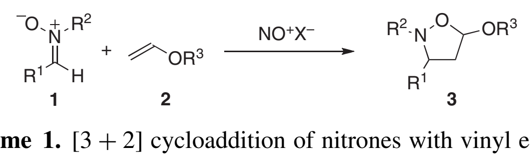
NO cations were found to be a highly effective catalysts in several carbon–carbon bond forming reactions. For example, [3 + 2] cycloadditions of nitrones or azomethine imines with vinyl ethers proceeded in the presence of 0.1–1 mol % of the NO cation to afford the desired adducts in high yields.

The nitrosonium (NO) cation is an inorganic but nonmetallic and is neither Brønsted acidic nor basic.[1] While the NO cation is well known in inorganic chemistry as an effective coordinating ligand as well as an effective electron-withdrawing group, the application of NO cations to organic synthesis as catalysts has been quite limited despite its highly active nature.[2] In recent organic synthesis, the use of metal compounds is sometimes avoided because of harmful waste generated after the reaction. Although nonmetal activators, such as organocatalysts, have been developed, their catalytic activity in some cases is not so high. In our investigation of molybdenum or tungsten Lewis acid chemistry,[3] we were interested in the enhancement of Lewis acidity of the metal complexes using NO cations as a coordinative ligand.[4] During this study, we also found that the NO cation itself could work as a catalyst.[5] Here we report the NO cation catalyzed, highly efficient, carbon–carbon bond forming reactions including [3 + 2] cycloaddition reactions.

[3 + 2] cycloaddition of nitrones is an important method for synthesis of isooxazolidine derivatives, which can be converted to 1,3-amino alcohols by simple reductive cleavage of the N–O bond (Scheme 1). It has been reported that several activators, such as metal catalysts, promote this cycloaddition,[6] however efficiency of this reaction is not necessarily satisfactory compared with that of other reactions. We investigated the reaction of nitrones derived from benzaldehyde and *N*-phenylhydroxylamine with *tert*-butyl vinyl ether in the presence of a catalytic amount of $NOPF_6$, and the desired cycloadduct was obtained in high yield (Table 1, Entry 1).[7] Nitrones prepared from aromatic aldehydes bearing electron-donating groups reacted with the vinyl ether to afford the cycloadducts in high yields in the presence of 0.5–1 mol % of $NOPF_6$. The diastereoselectivities were almost the same as those of the reactions using the nitrone derived from benzaldehyde (Entries 2 and 3). Nitrones bearing electron-withdrawing groups also gave good results without any side reaction (Entries 4–6). Nitrones containing other aromatic rings, 1-naphthyl and 2-furyl groups, also reacted to afford the desired cyclic adducts in good yields (Entries 7 and 8). Not only aromatic but also α,β-unsaturated substituents were accommodated by this reaction (Entry 9), an aliphatic nitrone also reacted in good yield (Entry 10). We also examined the effect of the nitrones bearing substituted aromatic or aliphatic groups on the nitrogen atom. The electron-withdrawing group, *p*-chlorophenyl, gave similar results (Entry 11), although a significant decrease in reactivity was observed in the reaction of a nitrone with an electron-donating substituent, *p*-methoxyphenyl, on the nitrogen atom (Entry 12). A nitrone with a benzyl group reacted but in low yield and selectivity (Entry 13).



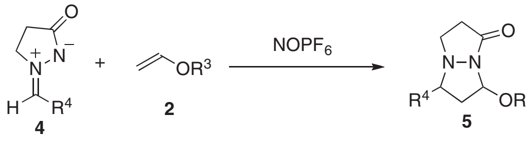
Scheme 1. [3 + 2] cycloaddition of nitrones with vinyl ethers.

Table 1. [3 + 2] cycloadditions of nitrones **1** with *tert*-butyl vinyl ether (**2a**) in the presence of a catalytic amount of $NOPF_6$[a]

Entry	R^1	*x*/mol %	Conditions	Y/%[b]	Dr[c]
1[d]	Ph	0.1	1 h, 1.0 M	90	78/22
2	$4\text{-}MeC_6H_4$	0.5	1 h, 0.5 M	96	82/18
3[e]	$4\text{-}MeOC_6H_4$	1	21 h, 0.25 M	92	86/14
4	$4\text{-}ClC_6H_4$	1	3 h, 0.17 M	84	84/16
5[e]	$4\text{-}FC_6H_4$	1	1 h, 0.17 M	95	83/17
6	$4\text{-}MeO_2CC_6H_4$	1	6 h, 0.17 M	79	85/15
7	1-Naphthyl	1	1 h, 0.25 M	77	76/24
8	2-Furyl	0.5	3 h, 0.25 M	94	84/16
9	Cinnamyl	1	1 h, 0.25 M	96	84/16
10	Cyclohexyl	0.5	1 h, 0.25 M	96	56/44
11[f]	Ph	1	1 h, 0.25 M	89	84/16
12[g]	Ph	1	1 d, 0.25 M	<3	—
13[h]	Ph	5	13 h, 0.25 M	38	66/34

[a] The reaction was carried out in CH_2Cl_2 at 0 °C using nitrones (R^2 = Ph) and **2a** in the presence of $NOPF_6$ (*x* mol %) unless otherwise noted. [b] Isolated yield. [c] Dr = trans/cis. [d] MS 3A was used. [e] At −30 °C. [f] R^2 = $4\text{-}ClC_6H_4$. [g] R^2 = $4\text{-}MeOC_6H_4$. [h] R^2 = Bn.

Next we turned our attention to development of other reactions using NO cations as the catalyst. Azomethine imines prepared from aldehydes and 3-pyrazolidinone have been shown to be good 1,3-dipoles in [3 + 2] cycloaddition reactions;[8] however, to the best of our knowledge, no successful example of the reaction using electron-rich olefins such as simple vinyl ethers has been reported (Scheme 2) despite some reactions using alkynes or α,β-unsaturated carbonyl compounds as substrates. First, a [3 + 2] cycloaddition reaction of an azomethine imine prepared from benzaldehyde with a vinyl ether was examined. The reaction with *tert*-butyl vinyl ether proceeded well in the



Scheme 2. [3 + 2] cycloaddition reaction of azomethine imine **4** with vinyl ether **2**.

Table 2. [3 + 2] cycloaddition of azomethine imine **4** and **2** in the presence of a catalytic amount of $NOPF_6$[a]

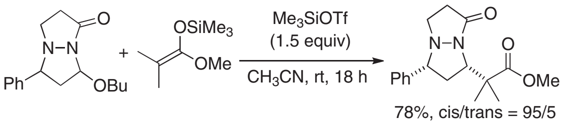
Entry	R^4	x/mol %	Time/h	Y/%[b]	Dr[c]
1	Ph	1	6	80	92/8
2	Ph	0.5	18	77	91/9
3[d,e]	Ph	5	24	84	54/46
4[f,g,h]	Ph	1	30	92	56/44
5	4-ClC_6H_4	1	20	80	87/13
6	4-FC_6H_4	1	18	82	85/15
7	4-$MeOC_6H_4$	3	18	78	90/10
8	4-MeC_6H_4	1	18	77	93/7
9	1-Naphthyl	1	7	75	89/11
10	5-Me-2-furyl	1	48	32	80/20
11	Cinnamyl	5	48	48	86/14
12	Cyclohexyl	1	24	76	70/30
13	*t*-Bu	1	24	80	85/15
14[g,h]	*i*-Bu	1	22	75	44/56
15[g,h]	Pr	1	20	63	47/53

[a]The reaction was carried out in CH_2Cl_2 at 0 °C using azomethine imine **4** and **2a** (1.5 equiv) in the presence of $NOPF_6$ (x mol %) unless otherwise noted. The concentration was 0.25 M. [b]Isolated yield. [c]Dr = cis/trans. [d]At rt. [e]Dihydrofuran (**2c**) was used instead of **2a**. [f]0.5 M. [g]At 20 °C. [h]Butyl vinyl ether (**2d**) was used instead of **2a**.

presence of 1 mol % of $NOPF_6$ to afford the desired bicyclic adduct in good yield with good diastereoselectivity (Table 2, Entry 1). The same reaction also proceeded in the presence of 0.5 mol % of the NO cation (Entry 2). We then investigated reactions using other vinyl ethers. The reaction with dihydrofuran and butyl vinyl ether proceeded in good yield but with low diastereoselectivity (Entries 3 and 4). The reactions of other azomethine imines were also investigated. Azomethine imines bearing electron-withdrawing groups (Cl and F) reacted with the vinyl ether in good yields with good diastereoselectivities (Entries 5 and 6). A slightly negative effect was observed when imines with electron-donating substituents were employed, but the conversions were still good (Entries 7 and 8). Imines containing other aromatic groups, 1-naphthyl and 5-methyl-2-furyl, were also employed. The reaction proceeded well in the case of the naphthalene imine (Entry 9), however, the yield was only moderate in the 5-methyl-2-furyl case (Entry 10). The cinnamyl imine also reacted but conversion was not good (Entry 11). The effect of alkyl substituents was then investigated, and good yields were obtained in the reactions with cyclohexyl and *t*-Bu derivatives (Entries 12 and 13). This method provides an efficient synthesis of the hexahydropyrazolo[1,2-*a*]pyrazole ring system.

Further transformation of the bicyclic products obtained in the reactions of the azomethine imines with vinyl ethers has been demonstrated. A reaction with a ketene silyl acetal was conducted in the presence of trimethylsilyl triflate, and the resulting adduct was obtained with high diastereoselectivity (eq 1).[9] Moreover, the N–N bond was successfully cleaved under reductive conditions (eq 2).[10]

In summary, we have found that NO cations work well as a nonmetal, inorganic catalyst for carbon–carbon bond forming reactions.[11] Nitrones and azomethine imines successfully reacted with vinyl ethers in high yields with high diastereoselectivities. Only 0.1–1 mol % of the NO cation was sufficient to promote the transformation efficiently. It is noted that the cycloaddition of the azomethine imine with vinyl ethers is a new method to construct a hexahydropyrazolo[1,2-*a*]pyrazole ring system with N,O-acetal moiety. Further studies on the mechanism of the catalysis and applications to other reactions are in progress.[12]



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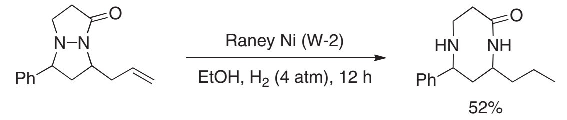

(2)

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11 The NO cation can also promote a Mannich-type reaction, a Mukaiyama aldol reaction, and a 1,4-addition reaction of a silicon enolate. See Supporting Information.

12 A preliminary study on the mechanism of these reactions is shown in Supporting Information. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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